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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food & Drug Administration
300 Pearl Street, Suite 100
Buffalo, NY 14202
TEL. (716) 551-4461

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

27 August 1998

WARNING LETTER BUF 98-12

Mr. John D. Barlow, Jr., President & CEO
Ethox Corporation
251 Seneca Street
Buffalo, New York 14204

Dear Mr. Barlow:

An inspection of your facility at 251 Seneca Street, Buffalo, NY was conducted by Food and Drug Administration (FDA) Investigator Joseph A. Famiglietti from 15 June through 20 July 1998. The inspection revealed [REDACTED] disposable infusion sets manufactured at your facility are adulterated within the meaning of Section 501(h) of the Federal Food, Drug and Cosmetic Act (the Act).

These infusion sets are medical devices, and are adulterated because the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation were not in conformance with the current Good Manufacturing Practice (CGMP) requirements of the Quality System Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820. The 1978 Good Manufacturing Practice (GMP) for Medical Devices regulation was superseded on June 1, 1997, by the Quality Systems Regulation. Since some of the records reviewed were dated prior to June 1, 1997, deficiencies related to those records are cross-referenced to the corresponding 1978 GMP. CGMP deviations noted include the following:

- failure to take adequate corrective actions after identifying the cause of broken ports on the [REDACTED] heat exchanger assembly [21 CFR 820.100], even though the broken ports had been the subject of multiple product complaints. This failure would have been a deviation from the 1978 GMP regulations under 820.20(a)(3).
- failure to ensure all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed and installed to facilitate maintenance, adjustment, cleaning and use; for example, installation qualification studies

have not been done for the [REDACTED] sealer used to seal, and reseal, pouches for the [REDACTED] sets [21 CFR 820.70(g)].

- failure to adhere to established process control procedures (equipment set-up parameters) necessary to ensure conformance to specifications [21 CFR 820.70]; tub sealing equipment was qualified for operating at 295 degrees F. and 90 psi with an 8 second dwell time. Parameters in use from 6/5/97 through 12/12/97 were found to range from 300 to 318 degrees F. with dwell times ranging from 6.5 to 12 seconds.
- inappropriate release and use of non-conforming product; Lot 1712536 of [REDACTED] sets was released despite the fact tub-to-lid seals failed to meet burst test requirements and fell below specification for seal dimensions. The lot was released without an appropriate written justification, and written procedures for release of non-conforming product were not followed [21 CFR 820.90].
- failure to recognize, and review as a non-conformance, a below-specification test result for the [REDACTED] burst testing performed 5/14/98 to evaluate tub/lid seal integrity of [REDACTED] sets (MSO 309445); the test result of "8.4" recorded in the device history record falls below the minimum acceptable burst pressure specified in the device master record; This was not identified as an out-of-spec result and the lot was subsequently released without reviewing this as a non-conformance [21 CFR 820.90].
- failure to establish and implement written procedures for evaluating non-conformances due to burst test failures of the tub/lid seals or due to low seal width measurements [21 CFR 820.90].
- failure to follow written procedures for investigating and documenting [REDACTED] burst testing failures reported in Non-Conforming Material Report (NCMR) 15388; Ethox SOP requires an explanation of the cause of the non-conformance be included in the NCMR, but no explanation was included [21 CFR 820.90].
- failure to establish and implement written procedures for rework, to include retesting and reevaluation of the non-conforming product after rework; According to NCMR 15388, pouches (labeled as sterile) which initially failed to meet burst test specifications, were subsequently reworked and released [21 CFR 820.90(b)].
- the QC sampling procedure for checking pouch seals, and tub/lid seals, is inadequate because it fails to assure adequacy of seals throughout the entire shift; Instances were noted where only one check per shift was performed [21 CFR 820.70].

I received your letter of 22 July 1998 responding to deficiencies pointed out at the conclusion of our inspection. It has been made a part of the official file maintained for your firm and will be considered with other records there. Your letter adequately addresses most of the deficiencies noted

during the inspection. However, your response does not adequately address corrective action for the following:

- Your response to observation 6, while admitting an out-of-spec burst test result was overlooked, does not address what if any actions have been or will be taken to bring the lot, which was released and distributed, into compliance.
- Your response to observation 5b and 7 indicate your firm considers deviations from "internally imposed" specifications (such as burst test failures of sealed pouches) to be less significant than "customer specified requirements", in that written customer approval is not required for deviations from internal specifications. Your firm is required to manufacture the product in compliance with all appropriate GMP requirements, regardless of whether the contracting firm provides written specifications. This is particularly significant in light of the fact you lack a written contract clearly identifying requirements and responsibilities related to the manufacture of the [REDACTED] product.
- Regarding your response to observation 11, your sampling schedule must be based on a sound statistical rationale, not merely on the length of the process run. Even after installation qualification of the sealing equipment is completed, an appropriate sampling schedule must be established and followed.
- Your response to observation 5d indicates your firm will be conducting a [REDACTED] of a [REDACTED]. Your response addresses the writing, [REDACTED] but does not mention [REDACTED].

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violation and deficiencies noted in this letter and in the FDA-483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your establishment's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for Class III devices to which the GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject device have been corrected.

You should take prompt action to correct this violation, and all other violations existing at your firm. Failure to achieve prompt corrective action may result in regulatory action - without further notice. This action may include, but is not limited to, seizure, injunction and/or civil penalties.

Please notify this office, in writing, within 15 days, of the specific steps you have taken, or intend to take, to correct this violation. Your response may be directed to James M. Kewley, Compliance Officer, at the above address.

Sincerely,


Brenda J. Holman
District Director

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cc:

[Redacted]